



## University of Dundee

### Translational genetics

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*Published in:*  
British Journal of Dermatology

*DOI:*  
[10.1111/bjd.19618](https://doi.org/10.1111/bjd.19618)

*Publication date:*  
2020

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Brown, S. J. (2020). Translational genetics: a challenging but important path. *British Journal of Dermatology*.  
<https://doi.org/10.1111/bjd.19618>

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## Translational genetics: a challenging but important path

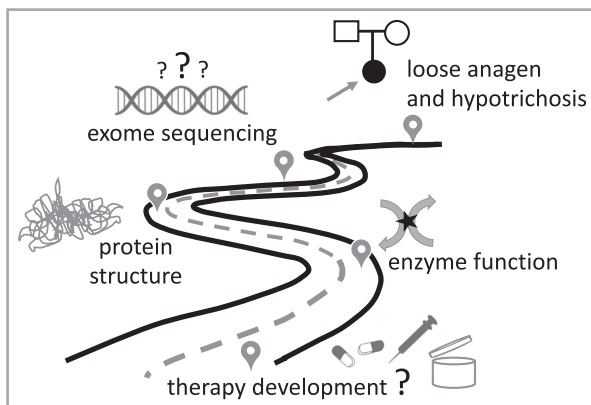
DOI: 10.1111/bjd.19618

**Linked Article:** Onoufriadis *et al.* *Br J Dermatol* 2020; <https://doi.org/10.1111/bjd.19481>

Hair disorders can be difficult to address in clinic, not least because our current understanding of molecular mechanisms and targeted therapies remains limited. Loose anagen syndrome (OMIM 600628) is reportedly rare, although cases may remain undiagnosed because the condition is usually self-limiting. A genetic predisposition with dominant inheritance has been observed<sup>1</sup> and the shed hairs may be thinner and longitudinally grooved.<sup>2</sup> It has therefore been suggested that variation in *KRT75* (OMIM \*609025), encoding a keratin of the inner root sheath companion layer, may account for loose anagen and unruly hair.<sup>3</sup>

Onoufriadis *et al.*<sup>4</sup> propose a genetically determined enzyme abnormality to account for loose anagen occurring with hypotrichosis. Recessive mutations in *TKFC*, the gene encoding an enzyme named trikinase and flavin mononucleotide cyclase, were detected in one compound heterozygous case, from a total of 15 families studied. This gene product has not previously been implicated in skin or hair disorders and the protein structure has not been determined by crystallization. The conclusion that *TKFC* plays a role in loose anagen syndrome therefore required a sequence of work from genetic analysis to functional assessment of enzyme variants (Figure 1).

Whole-exome sequencing (WES) has been used to identify genes responsible for a range of dermatological disorders,<sup>5</sup> but sequence analysis data must be carefully interpreted and various assumptions are required to make sense of the large number of variants detected. Onoufriadis *et al.*<sup>4</sup> applied WES to 15 families with children showing features of loose anagen.



**Figure 1** The challenging path of investigation from a patient with genetic disease to possible therapy development.

The pattern of inheritance was assumed to represent a new dominant mutation or recessive mutations, the variant(s) should be rare (present in < 0.5% of individuals in available databases), and variant(s) should have a deleterious effect on the protein product, based on biochemical structure or function predictions. The team were lucky in that only one gene met all of these criteria, because multiple plausible mutations can be detected even in apparently healthy individuals,<sup>6</sup> each requiring detailed characterization. Modelling *in silico* and functional analyses *in vitro* were next used to confirm the effects of compound heterozygous mutations in *TKFC* on enzyme function. Onoufriadis and colleagues are to be congratulated on completing this detailed and technically challenging work. Further steps towards a therapeutic intervention are clearly a possibility.

Questions remain unanswered in this path from phenotype to genotype to molecular mechanisms. Why is hair on the scalp preferentially affected by this metabolic defect and why is loose anagen a self-limiting disorder? To what extent does *TKFC* contribute to the hypotrichosis seen in this patient in addition to loose anagen? Why were *TKFC* variants not found in any of the other families with a similar hair phenotype? These observations indicate that functional variants in *TKFC* are likely to be a rare cause even within a rare disorder, thereby limiting wider therapeutic use. The authors acknowledge that other *TKFC* variants cause multisystem disease without a hair disorder;<sup>7</sup> genetic variation in or near *TKFC* may also contribute to the control of skin and hair pigmentation in African populations.<sup>8</sup> It is plausible that different mutations give rise to different phenotypes, or the transient effects of loose anagen may simply have been overlooked.

Despite these unanswered questions, the work by Onoufriadis and colleagues is an exemplar for translational genetics. It demonstrates the important opportunity to identify previously unexpected molecular mechanisms of dermatological disease for future therapeutic targeting.

**Acknowledgments:** I am grateful to Professor Edel O'Toole for her expert review of this commentary.

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**Funding sources:** Wellcome Trust Senior Research Fellowship (reference 106865/Z/15/Z).

**Conflicts of interest:** The author declares they have no conflicts of interest.

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